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CLINICAL STUDIES

Coronary Hemodynamics and Myocardial Metabolism in Patients With Syndrome X: Response to Pacing Stress

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Coronary hemodynamics, myocardial metabolism and left ventricular function at rest and after incremental atrial pacing were evaluated in 12 patients with stress-induced angina and ST segment depression, angiographically normal coronary arteries and no evidence of spasm, generally labeled as syndrome X, and in 10 normal subjects.

At baseline study, great cardiac vein flow was comparable in patients and control subjects. During pacing, an equivalent rate-pressure product was reached in the two groups, but the slope of the relation between rate-pressure product and great cardiac vein flow was significantly less steep in patients than in normal subjects (0.0027 vs. 0.0054 ml/mm Hg·beat, $p < 0.001$). Nevertheless, the left ventricular ejection fraction was comparable in both groups at rest (66 ± 6% vs. 71 ± 7%, p = NS) and during pacing (71 ± 7% vs. 66 ± 5%, p = NS).

At baseline study, myocardial glucose extraction was more efficient in patients with syndrome X ($p < 0.05$), but net myocardial exchange of pyruvate and alanine was, respectively, smaller and greater than in control subjects. Lactate was extracted to a similar extent in the two groups and in no instance was net lactate release observed during pacing or recovery. During pacing and recovery, patients with syndrome X showed net pyruvate release, unlike the control subjects in whom net pyruvate exchange was positive. In addition, patients with syndrome X continued to show net myocardial extraction of alanine during pacing and recovery, whereas normal subjects produced alanine throughout the study.

Myocardial carbohydrate oxidation increased significantly during maximal pacing in normal subjects but not in patients, in whom it always remained below ($p < 0.01$) the concurrent rate of myocardial uptake of carbohydrate equivalents (glucose, lactate, pyruvate, alanine). Myocardial energy expenditure was significantly lower in patients than in control subjects at maximal rate-pressure product levels ($p < 0.01$).

The metabolic pattern in patients with syndrome X therefore is not consistent with classic ischemia, although differences in the net exchange of circulating substrates (glucose, pyruvate, alanine) can be demonstrated. Thus, in patients with syndrome X, the symptoms, electrocardiographic signs and impairment in the increase in great cardiac vein flow during pacing coexist with preserved global and regional left ventricular function and myocardial energy efficiency.

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A sizable proportion of patients undergoing coronary arteriography for a chest pain syndrome are found to have normal coronary arteries. Although in some patients the pain syndrome may be of noncardiac origin, many patients have typical anginal episodes often accompanied by electrocardiographic (ECG) changes. Myocardial ischemia is generally considered the cause of angina in these patients, and a reduced vasodilator reserve of the small coronary arteries has been proposed as the mechanism (1,2). However, there is conflicting evidence about the efficacy of standard antiischemic drugs (beta-receptor blocking agents, nitrates and calcium channel blockers) in patients with chest pain and normal coronary arteries (3–6), who also appear to have a good long-term prognosis (7,8).

Among patients with angina and angiographically normal coronary arteries, a group with ischemic ECG changes during exercise can be identified. These patients—generally labeled as having syndrome X (stress-induced angina and ST segment depression, angiographically normal coronary arteries and no evidence of spasm of epicardial vessels)—represent a small and clinically homogeneous subset of the rather heterogeneous pool of patients with chest pain and normal coronary arteries.

To further elucidate the pathophysiologic mechanisms of this disease, coronary hemodynamics, left ventricular function and myocardial metabolism were investigated at rest and during atrial pacing in a group of patients with syndrome X and a group of normal subjects.

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Table 1. Characteristics of the Study Group

	Age (yr)/ Gender	Blood Pressure (mm Hg)		Exercise Stress Test			Study Protocol	
		SBP	DBP	ST (mV)	RPP (mm Hg · beats/min)	Pain	Baseline	Stress
Syndrome X								
1	45/F	106	66	0.20	28,000	+	+	+
2	56/F	118	76	0.25	30,000	+	+	+
3	59/F	127	77	0.15	28,900	+	+	+
4	55/F	113	73	0.15	30,400	+	+	+
5	48/F	125	84	0.20	23,300	+	+	+
6	57/F	119	73	0.20	22,300	+	+	+
7	51/F	124	81	0.15	35,700	+	+	+
8	52/F	131	84	0.15	30,600	+	+	+
9	54/F	119	76	0.15	20,800	+	+	+
10	43/F	116	79	0.15	18,000	+	+	−
11	41/F	113	69	0.15	26,400	+	+	−
12	46/F	115	76	0.15	24,400	+	+	+
Mean	50	118	76	0.17	26,566			
± SD	6	7	5	0.03	4,777			
Normal subjects								
1	43/M	105	65	0	32,400	−	+	+
2	45/M	105	70	0	38,800	−	+	+
3	59/F	120	80	0	21,500	−	+	+
4	51/M	110	70	0	21,000	−	+	+
5	51/F	112	73	0	19,950	+	+	+
6	44/M	125	80	0	29,600	−	+	+
7	57/F	114	76	0	16,200	−	+	−
8	50/F	107	82	0	25,500	−	+	−
9	47/M	99	69	0	21,000	+	+	−
10	55/M	100	79	0	18,600	−	+	−
Mean	50	109	74		24,455			
± SD	5	8	5		6,721			

Mean values for systolic (SBP) and diastolic (DBP) blood pressure were recorded during 7 days of hospitalization. Baseline = hemodynamic and metabolic measurements under baseline conditions; F = female; M = male; RPP = rate-pressure product; ST = ST segment depression from baseline during the stress test; Stress = hemodynamic and metabolic measurements during pacing and recovery; − = no; + = yes.

Methods

Study subjects (Table 1). *Patients with syndrome X.* Of 712 consecutive in-patients who underwent coronary arteriography at our institution from January 1986 to March 1989 to evaluate a chest pain syndrome, 146 (20.5%) were found to have normal coronary arteries. However, most of these patients had a cardiac or extracardiac disease that could explain the chest pain syndrome or had normal findings on an exercise stress test. Only 18 of the 146 patients (that is, 12% of those with normal coronary arteries or 2.5% of the entire group) had ST segment depression on the ECG during exercise-induced angina and normal result on an ergonovine test. Twelve of these 18 patients were enrolled in the study. They were all women (mean age 50 years, range 41 to 59) and had a normal physical examination, chest X-ray series and echocardiogram. The ECG at rest was normal in 10 patients and showed nonspecific disturbances of ventricular repolarization (flat and low voltage negative T waves) in 2, but none of the patients had conduction abnormalities. All had a positive exercise stress test (horizontal or downsloping ST segment depression >0.15 mV of the baseline value 0.08 s after the J point) with angina and normal coronary and left ventricular angiograms (Table 1).

Normal subjects. Six men and four women (mean age 50 years, range 43 to 59) were evaluated for a chest pain syndrome. All had normal results on physical examination, rest ECG, chest X-ray series, echocardiogram, exercise stress test and coronary and left ventricular angiogram.

The ergonovine test (scalar doses starting from 0.025 mg up to 0.20 mg intravenously) was negative for symptomatic and ECG criteria in both groups. No subject in either group had diabetes mellitus, hyperlipidemia, arterial hypertension, mitral valve prolapse, primary myocardial disease or other cardiac or extracardiac disease. A period of pharmacologic washout of ≥72 h was allowed before the study (no patient was taking a beta-blocker before entering the study). The protocol of the study was approved by the local Ethics Committee. Each subject was informed of the investigative nature of the study and written consent was obtained before entry.

Study protocol. All subjects were studied after an overnight fast of 12 to 15 h. Selective left and right coronary

angiography in multiple views was performed with the Judkins technique. At least 30 min was allowed between coronary angiography and the beginning of the study to minimize any possible interference of the contrast medium with myocardial metabolism (9). Great cardiac vein flow was measured by the thermodilution technique (10,11). Aortic and left ventricular pressures (fluid-filled method) and the six standard ECG limb leads and one precordial ECG lead were continuously monitored and, when needed, recorded on paper together with the flow measurements by means of a 12 channel recorder (OTE Biomedica).

Paired arterial and great cardiac vein blood samples were simultaneously drawn in duplicate during basal conditions. One sample (1 ml) was used for blood gas determination and one (2.5 ml) for the assay of glucose, free fatty acids, lactate, pyruvate, alanine, beta-hydroxybutyrate and glycerol, as described elsewhere (12). Thereafter, subjects underwent up to four pacing steps of 4 min duration, with heart rate increments of 15 beats per step for the first three steps and up to maximal heart rate achievable (exacerbation of symptoms or occurrence of atrioventricular conduction disturbances, or both) on the last step (no atropine was used). During each pacing period, 2 min was allowed to achieve a steady state condition. Arterial and great cardiac vein blood samples were then obtained and pressures and great cardiac vein flow recorded. Blood sampling and hemodynamic measurements were repeated 1, 5, 10, 15 and 25 min after the end of pacing. At the end of the study, biplane left ventriculography was performed during basal conditions and at the maximal heart rate achieved with pacing.

The measurements at rest were obtained in all 10 subjects in the control group, but only 6 (2 women, 4 men) completed the entire study. Of the 12 patients with syndrome X, all had basal measurements taken and 10 completed the pacing/recovery protocol. However, one of these latter patients (Patient 12) was subsequently excluded from the data analysis because of an abnormal oral glucose tolerance test (Table 1).

Data analysis. Ventricular function was evaluated on angiographic images by a computer-assisted method that allows analysis of regional wall motion and computes left ventricular ejection fraction by the area-length method (13). Coronary resistance was calculated as the mean arterial pressure divided by great cardiac vein flow. The rate-pressure product was calculated by multiplying heart rate by aortic systolic pressure. Myocardial oxygen consumption and carbon dioxide production were obtained from the respective arteriovenous differences multiplied by great cardiac vein flow and were expressed as μmol/min. The respiratory quotient was calculated as the carbon dioxide production/oxygen consumption ratio. Net rates of carbohydrate and lipid oxidation and myocardial energy expenditure were calculated from gas exchange measurements by using calorimetric equations (14).

The fractional extraction (E) of each substrate was computed according to the formula: E = [(SA − SGCV)/SA] × 100, where SA and SGCV are the substrate concentrations in arterial and great cardiac vein blood, respectively. Net myocardial exchange (uptake or release) of substrates was computed as (SA − SGCV) × great cardiac vein flow (μmol/min). Total carbohydrate uptake was calculated as the algebraic sum of the net exchange of glucose and three carbon compounds (lactate, pyruvate and alanine, expressed as glucose equivalents). The complete technical details about the different procedures used in this study have been previously reported (12).

Statistics. All data are expressed as the mean values ± standard deviation of the mean (SD). Two-way analysis of variance was used to assess differences in mean values between the study groups while simultaneously accounting for changes due to protocol (that is, pacing and recovery steps). Intergroup comparison of individual time points was carried out with use of the unpaired t test. For intragroup comparison of individual time points, the paired t test was used. Linear regression was computed by standard methods. Comparison of regression slopes was carried out by t test analysis. A p value <0.05 was considered significant.

Results

Typical chest pain and ST segment depression (>0.15 mV) were observed during atrial pacing in all the patients with syndrome X, but in none of the normal subjects.

Hemodynamic variables (Table 2). Comparable heart rates were reached during atrial pacing in patients and control subjects. Although the subjects in the two groups were equally normotensive (as shown by the mean pressure values recorded four times daily during 1 week of hospitalization [Table 1]), aortic systolic pressure measured at the time of the invasive study was 12% higher ($p < 0.05$) in the patients with syndrome X than in the control subjects. Left ventricular end-diastolic pressure was within normal limits in both groups at baseline and during and after pacing stress, with consistently lower values in patients with syndrome X ($p < 0.05$). The rate-pressure product and great cardiac vein flow were comparable in the two groups at baseline. Great cardiac vein flow increased somewhat less in the patients than in the control subjects at the higher pacing rates, although this difference was not statistically significant ($p = 0.08$) (Table 2). However, the slope of the relation between the rate-pressure product and great cardiac vein flow during pacing in patients with syndrome X was half that of the normal subjects (0.0027 vs. 0.0054 ml/mm Hg·beat, $p < 0.001$) (Fig. 1).

The left ventricular ejection fraction was comparable in normal subjects and patients with syndrome X at rest (71 ± 7% vs. 66 ± 6%, p = NS). During atrial pacing, the ejection fraction was unchanged in normal subjects (66 ± 5%, p = NS compared with the rest value), whereas it increased slightly in patients with syndrome X (71 ± 7%, $p < 0.05$ vs. baseline and p = NS vs. pacing value in normal subjects). Left ventricular volumes decreased in both groups during atrial

Table 2. Hemodynamic Variables During Cardiac Catheterization

	Heart Rate (beat/min)		Systolic Pressure (mm Hg)		Diastolic Pressure (mm Hg)		LV End-Diastolic Pressure (mm Hg)	
	N	X	N	X	N	X	N	X
B	76 ± 14	77 ± 9	124 ± 16	139 ± 21	74 ± 13	76 ± 11	5.5 ± 3.3	3.8 ± 2.7
P1	100 ± 14	100 ± 6	132 ± 16	149 ± 21	79 ± 13	84 ± 11	6.5 ± 4.1	3.1 ± 3.0
P2	116 ± 15	114 ± 5	137 ± 17	148 ± 22	83 ± 12	86 ± 10	5.8 ± 4.1	2.8 ± 3.3
P3	131 ± 18	132 ± 7	134 ± 15	144 ± 23	86 ± 17	87 ± 9	6.7 ± 3.4	2.7 ± 2.7
Pmax	157 ± 14	157 ± 16	152 ± 16	150 ± 29	89 ± 15	92 ± 11	7.8 ± 5.8	2.3 ± 2.3
R1	82 ± 11	85 ± 13	130 ± 14	138 ± 19	76 ± 12	77 ± 11	9.7 ± 5.9	2.5 ± 2.1
R2	79 ± 12	87 ± 10	128 ± 19	140 ± 23	78 ± 12	77 ± 10	7.3 ± 4.2	2.6 ± 2.2
R3	79 ± 7	86 ± 12	131 ± 18	142 ± 23	76 ± 10	78 ± 10	7.5 ± 4.3	2.9 ± 2.1
R4	77 ± 8	87 ± 9	128 ± 19	143 ± 22	79 ± 11	79 ± 10	6.0 ± 3.8	2.6 ± 2.1
R5	78 ± 11	85 ± 11	123 ± 16	138 ± 21	76 ± 11	73 ± 5	5.5 ± 4.0	4.0 ± 2.5

	Great Cardiac Vein Flow (ml/min)		Rate-Pressure Product (mm Hg·beat/min/1,000)		Coronary Resistance (mm Hg/ml per min)	
	N	X	N	X	N	X
B	52 ± 16	56 ± 20	9.4 ± 2.2	10.8 ± 2.3	1.96 ± 0.69	1.91 ± 0.61
P1	67 ± 23	67 ± 24	13.2 ± 2.4	14.9 ± 2.5	1.60 ± 0.62	1.73 ± 0.53
P2	76 ± 17	77 ± 24	15.8 ± 2.5	16.9 ± 2.8	1.41 ± 0.38	1.51 ± 0.50
P3	103 ± 44	82 ± 31	17.4 ± 2.7	19.1 ± 3.3	1.14 ± 0.47	1.43 ± 0.48
Pmax	104 ± 30	90 ± 30	21.9 ± 2.2	23.3 ± 3.8	1.11 ± 0.51	1.32 ± 0.36
R1	72 ± 29	63 ± 26	10.6 ± 0.7	11.7 ± 2.2	1.47 ± 0.57	1.73 ± 0.61
R2	57 ± 18	56 ± 17	9.9 ± 1.0	12.2 ± 2.4	1.75 ± 0.44	1.97 ± 0.85
R3	53 ± 16	64 ± 27	10.2 ± 0.9	12.3 ± 2.9	1.91 ± 0.53	1.80 ± 0.70
R4	54 ± 20	58 ± 19	9.8 ± 0.8	12.5 ± 2.3	1.98 ± 0.82	1.88 ± 0.61
R5	54 ± 19	46 ± 15	8.9 ± 1.3	11.6 ± 2.2	1.86 ± 0.60	2.11 ± 0.71

All values are mean values ± SD. LV = left ventricular; N = normal subjects; P = to Pmax = pacing (P) steps from baseline (B) to maximal pacing (Pmax) to the recovery (R) phase; X = patients with syndrome X.

Figure 1. Individual values of rate-pressure product (RPP) from baseline study to maximal pacing plotted against the respective values of great cardiac vein (GCV) flow in normal subjects (left) and patients with syndrome X (right). A significant linear relation between rate-pressure product and great cardiac vein flow was found in both groups during atrial pacing. However, the slope of this relation in normal subjects was twice that in patients with syndrome X ($p < 0.001$).

pacing. End-diastolic volume decreased by 16 ± 16% in normal subjects and by 20 ± 15% in patients (p = NS); end-systolic volume decreased by 18 ± 21% and 27 ± 13%, respectively (p = NS). No regional wall motion abnormalities were detected in normal subjects or patients with syndrome X at baseline or during atrial pacing.

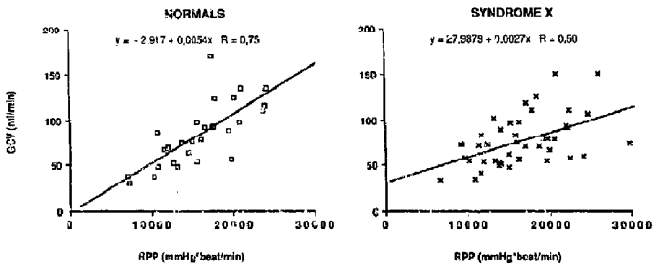

Table 3. Myocardial Exchange of Oxygen and Carbon Dioxide During Pacing and Recovery

	Oxygen Extraction (%)		Oxygen Consumption (μmol/min)		Carbon Dioxide Production (μmol/min)		Respiratory Quotient		Energy Expenditure (calories/min)	
	N	X	N	X	N	X	N	X	N	X
B	71 ± 7	69 ± 3	301 ± 131	281 ± 104	225 ± 90	200 ± 87	0.76 ± 0.09	0.77 ± 0.15	31.7 ± 13.4	29.6 ± 10.6
P1	69 ± 6	66 ± 5	380 ± 134	324 ± 109	252 ± 95	203 ± 85	0.75 ± 0.15	0.74 ± 0.18	35.5 ± 10.2	33.6 ± 9.7
P2	67 ± 6	65 ± 7	402 ± 75	371 ± 128	312 ± 36	219 ± 97	0.83 ± 0.13	0.67 ± 0.16	41.3 ± 6.2	38.0 ± 12.6
P3	66 ± 7	63 ± 4	534 ± 175	383 ± 139	410 ± 149	252 ± 107	0.76 ± 0.07	0.73 ± 0.18	56.7 ± 19.0	40.0 ± 14.3
Pmax	64 ± 8	62 ± 4	560 ± 173	410 ± 121	498 ± 173	312 ± 165	0.89 ± 0.15	0.70 ± 0.30	61.7 ± 19.1	42.5 ± 14.8
R1	67 ± 9	66 ± 6	397 ± 179	303 ± 118	295 ± 153	161 ± 55	0.74 ± 0.14	0.62 ± 0.17	41.8 ± 19.4	30.3 ± 10.8
R2	67 ± 1	65 ± 7	315 ± 111	266 ± 77	218 ± 90	194 ± 59	0.68 ± 0.12	0.78 ± 0.17	32.6 ± 11.8	28.2 ± 7.7
R3	68 ± 8	68 ± 6	293 ± 95	329 ± 129	218 ± 79	166 ± 60	0.74 ± 0.13	0.62 ± 0.15	30.9 ± 10.1	32.0 ± 12.6
R4	68 ± 7	67 ± 4	297 ± 115	289 ± 86	225 ± 79	195 ± 72	0.77 ± 0.12	0.76 ± 0.16	31.4 ± 11.6	30.4 ± 8.8
R5	67 ± 5	69 ± 6	293 ± 110	252 ± 81	205 ± 87	160 ± 39	0.69 ± 0.19	0.72 ± 0.11	30.1 ± 10.9	26.2 ± 7.9

All values are mean values ± SD. Abbreviations as in Table 2.

Exchange of oxygen and carbon dioxide (Table 3). Myocardial oxygen extraction was similar in the two groups at rest; in both, it tended to decrease during pacing. Myocardial oxygen consumption, comparable in the two groups at rest, was significantly lower in patients with syndrome X during pacing ($p < 0.01$). Likewise, myocardial carbon dioxide output at rest was similar between the two groups but was significantly lower in patients with syndrome X throughout the pacing and recovery periods ($p < 0.01$). The respiratory quotient was comparable in normal subjects and patients with syndrome X at baseline (0.76 ± 0.09 vs. 0.77 ± 0.15, p = NS), increased significantly in the former group at maximal pacing (0.89 ± 0.15, $p < 0.05$ vs. the rest value) and was unchanged in the latter (0.70 ± 0.30, p = NS).

Substrate handling (Table 4). No statistically significant differences between the two groups were found with regard to the arterial concentrations of measured substrates, which remained unchanged throughout the study. Overall, the myocardial fractional extraction of glucose was slightly greater in patients with syndrome X than in normal subjects

Table 4. Myocardial Percent Extraction Fraction of Substrates During Pacing and Recovery

	Glucose		Free Fatty Acids		Lactate		Pyruvate	
	N	X	N	X	N	X	N	X
B	1.3 ± 3.1	2.8 ± 2.0	24 ± 12.0	23 ± 8.1	32 ± 11.0	28 ± 14.0	40 ± 15.5	16 ± 27
P1	1.3 ± 3.0	2.1 ± 3.1	21 ± 17.5	19 ± 7.7	31 ± 16.5	31 ± 10.2	46 ± 9.5	14 ± 44
P2	2.8 ± 2.3	1.8 ± 4.3	23 ± 20.2	19 ± 15.8	32 ± 11.0	29 ± 9.7	42 ± 11.2	5 ± 34
P3	1.0 ± 2.1	2.2 ± 3.5	19 ± 14.2	22 ± 5.1	28 ± 10.3	31 ± 5.4	40 ± 8.3	6 ± 41
Pmax	1.9 ± 3.7	4.7 ± 2.8	26 ± 9.9	17 ± 7.1	28 ± 11.4	27 ± 11.7	34 ± 19.9	−48 ± 164
R1	2.9 ± 5.0	4.8 ± 3.0	24 ± 16.1	21 ± 8.3	36 ± 15.5	29 ± 10.4	36 ± 16.0	−6 ± 31
R2	2.7 ± 1.2	3.2 ± 3.9	25 ± 15.3	28 ± 29.4	32 ± 10.5	34 ± 19.4	32 ± 14.1	−20 ± 45
R3	2.6 ± 1.8	4.6 ± 3.4	14 ± 13.2	22 ± 8.9	31 ± 10.1	31 ± 13.7	35 ± 16.4	−17 ± 57
R4	4.4 ± 1.9	4.4 ± 3.4	17 ± 15.2	30 ± 27.1	29 ± 10.7	28 ± 19.4	34 ± 15.6	−20 ± 65
R5	2.5 ± 1.1	5.0 ± 2.4	20 ± 12.5	16 ± 16.2	30 ± 9.1	26 ± 13.9	37 ± 8.2	−82 ± 123

	Alanine		Beta-hydroxybutyrate		Glycerol	
	N	X	N	X	N	X
B	−3.5 ± 5.0	3.0 ± 8.7	40 ± 20	37 ± 13.4	3.8 ± 16.1	17 ± 13.6
P1	−4.2 ± 10.5	3.8 ± 8.5	31 ± 25	36 ± 8.1	9.0 ± 8.7	11 ± 15.9
P2	−0.2 ± 2.7	2.2 ± 8.9	38 ± 32	35 ± 8.2	2.9 ± 3.5	12 ± 13.2
P3	−1.5 ± 6.2	1.9 ± 9.6	49 ± 31	33 ± 6.5	12 ± 19.5	12 ± 16.9
Pmax	−1.5 ± 3.3	2.0 ± 8.6	30 ± 13	28 ± 7.4	2.5 ± 11.1	11 ± 8.7
R1	−1.5 ± 5.1	3.0 ± 12.4	14 ± 62	33 ± 4.8	2.0 ± 16.4	11 ± 17.7
R2	−3.6 ± 5.3	10.7 ± 26.1	32 ± 76	45 ± 15.3	7.2 ± 7.4	23 ± 23.3
R3	−2.0 ± 2.8	7.3 ± 17.0	21 ± 79	41 ± 9.8	12 ± 9.9	12 ± 18.9
R4	−4.7 ± 9.1	8.8 ± 21.2	7 ± 116	41 ± 14.9	4.2 ± 10.6	13 ± 22.5
R5	−4.6 ± 5.4	5.5 ± 13.8	−50 ± 244	47 ± 15.6	8.7 ± 9.2	21 ± 12.1

All values are mean values ± SD. Abbreviations as in Table 2.

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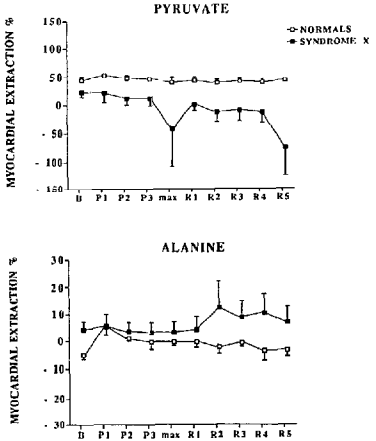

Figure 2. Pyruvate **(top)** and alanine **(bottom)** myocardial extraction in normal subjects and patients with syndrome X during the different study phases. In normal subjects, pyruvate is extracted and alanine is produced by the heart. In contrast, in patients with syndrome X, pyruvate extraction, lower than that in normal subjects at baseline study, is turned into net production during atrial pacing and recovery, whereas alanine is extracted throughout the study. B = baseline; P1 to max = pacing steps; R1 to R5 = recovery steps. Data are mean values ± SE.

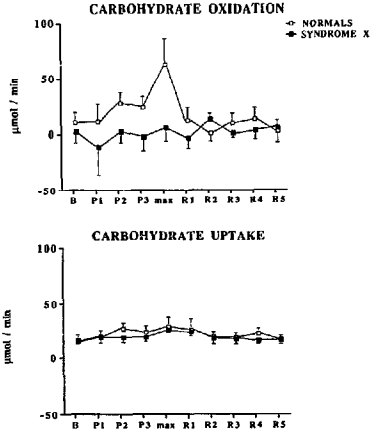

Figure 3. Carbohydrate (glucose + lactate ± pyruvate ± alanine) oxidation **(top)** and carbohydrate uptake **(bottom)** during the different study phases in normal subjects and patients with syndrome X. In both groups, carbohydrate uptake is substantial at baseline and during and after atrial pacing. In normal subjects, carbohydrate oxidation is increased significantly at maximal (max) pacing, whereas it is negligible in patients with syndrome X, despite a considerable uptake. Data are mean values ± SE. Abbreviations as in Figure 2.

($p < 0.05$). The extraction of free fatty acids, lactate and beta-hydroxybutyrate was similar in the two groups throughout the study. In no instance was net lactate production observed in normal subjects or patients with syndrome X. In addition, when myocardial lactate extraction was plotted against the rate-pressure product, a weak but significant positive correlation ($r = 0.36$, $p < 0.05$) was found in patients with syndrome X but not in normal subjects.

At rest, pyruvate extraction was lower in patients with syndrome X than in normal subjects ($p < 0.01$). In normal subjects, pyruvate was extracted by the myocardium during all the study steps, whereas a net pyruvate release was observed in patients with syndrome X at maximal pacing and throughout recovery ($p < 0.001$) (Fig. 2). In normal subjects, myocardial alanine extraction was negative (that is, there was a net release) at rest and during and after pacing stress. In contrast, the amino acid was consistently extracted by patients with syndrome X ($p < 0.001$) (Fig. 2). Myocardial extraction of glycerol was consistently higher in patients with syndrome X ($p < 0.01$) (Table 4).

At baseline study, the oxidation of carbohydrate fuel was very small in control subjects as well as in patients with syndrome X. In the former, carbohydrate oxidation increased significantly ($p < 0.05$) during maximal pacing to levels transiently exceeding the concurrent uptake of total carbohydrate equivalents. In contrast, in patients with syndrome X, carbohydrate oxidation was not stimulated by pacing and always remained below the concurrent rate of uptake of carbohydrate equivalents ($p < 0.01$ uptake vs. oxidation) (Fig. 3). Conversely, patients with syndrome X showed greater uptake of free fatty acids ($p < 0.05$) and greater oxidation of lipid fuel than normal subjects, although the latter difference fell short of statistical significance (Fig. 4).

Myocardial energy expenditure (Table 3) was similar in the two groups at baseline (31.7 ± 13.4 in normal subjects vs. 29.6 ± 10.6 cal/min [132.5 ± 56.0 vs. 123.7 ± 44.3 J/min] in patients with syndrome X), but was significantly lower in patients with syndrome X during maximal pacing (61.7 ± 19.1 vs. 42.5 ± 14.8 [257.9 ± 79.8 vs. 177.6 ± 61.9 J/min], $p < 0.01$) and returned to a comparable value during recovery (33.3 ± 13.0 vs. 29.7 ± 9.6 cal/min [139.2 ± 54.3 vs. 124.1 ± 40.1 J/min]; mean values for the entire recovery phase).

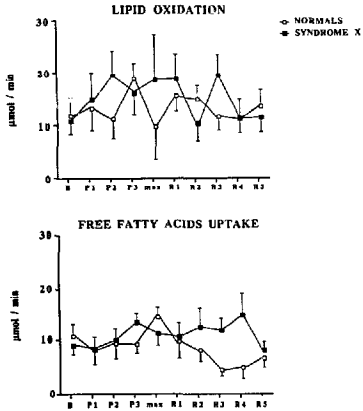

Figure 4. Lipid oxidation **(top)** and free fatty acid uptake **(bottom)** during the different study phases in normal subjects and patients with syndrome X. Free fatty acid uptake and lipid oxidation are greater in patients with syndrome X than in normal subjects. Data are mean values ± SE. Abbreviations as in Figure 2.

Discussion

Symptoms, Coronary Hemodynamics and Ventricular Function

Coronary hemodynamic and metabolic differences. In the rest state, the patients with syndrome X presented no significant hemodynamic changes relative to control subjects, except for a small difference in aortic systolic pressure. Heart rate, great cardiac vein flow, left ventricular end-diastolic pressure, coronary resistance, rate-pressure product, myocardial oxygen consumption, myocardial energy expenditure and the pattern of myocardial substrate oxidation (as reflected by the respiratory quotient) were essentially superimposable on those of the control subjects. Nevertheless, some metabolic differences were already present in patients with syndrome X at baseline in the absence of symptoms and ECG changes. In particular, glycerol was extracted more efficiently and pyruvate less efficiently in patients with syndrome X than in control subjects. Furthermore, a significant extraction of alanine occurred in patients with syndrome X in contrast to control subjects, in whom the transmyocardial extraction of this amino acid was negative (Table 4, Fig. 2).

Ischemic changes and ventricular function during pacing. Typical angina pectoris and ST segment depression similar to those observed during the exercise stress test were reproduced during atrial pacing in all patients with syndrome X. In addition, the slope of the relation between the rate-pressure product and great cardiac vein flow during pacing was significantly less steep in patients with syndrome X than in control subjects. The behavior of coronary flow during pacing was similar to that reported by Cannon and Epstein (2) in patients with microvascular angina, in whom it has been hypothesized that a functional abnormality of resistance vessels coexists with angiographically normal epicardial coronary arteries (1,2). Such behavior might explain the symptoms and ECG signs of ischemia observed in patients with syndrome X. However, if this interpretation might reconcile the clinical and anatomic data, it does not explain how patients experiencing typical symptoms and ECG signs of acute myocardial ischemia can have fully preserved global and regional left ventricular function. We cannot exclude that a stronger or different stress, or both, or the superimposition of a vasoconstrictor stimulus (such as the infusion of ergonovine) might have produced a larger flow deficit and functional abnormalities similar to those reported by Cannon et al. (15), although in our patients the stress of pacing was enough to produce typical angina and significant ST depression in all cases.

Our results are in agreement with those recently reported by Opherk et al. (8), who found normal left ventricular function (as assessed by gated blood pool scintigraphy) at rest and during exercise in patients with syndrome X. The follow-up study (8) demonstrated that left ventricular function was preserved over a 4 year period in patients who did not have conduction abnormalities but deteriorated significantly (>5% change in ejection fraction and progressive left ventricular dilation) in patients with rest or exercise-induced left bundle branch block. Patients with conduction disturbances were not included in our study.

Myocardial Metabolism

Lactate extraction, work, energy expenditure, carbohydrates and fatty substrates for oxidative metabolism during pacing. The metabolic data obtained during pacing and recovery in the patients with syndrome X did not show any change suggestive of myocardial ischemia. Unlike patients with atheromatous coronary artery disease, in whom myocardial lactate is released during pacing-induced ischemia (16–18), in our patients with syndrome X, net lactate release was never observed and a positive rather than negative relation between cardiac work and lactate extraction was seen. In contrast, net lactate release has been reported (8) in patients with rest or exercise-induced left bundle branch block and progressive deterioration of left ventricular function. Patients with syndrome X were able to carry out the same external work (rate-pressure product) with a smaller increment in blood flow, oxygen consumption (without increasing oxygen extraction) and energy expenditure than that measured in control subjects. To sustain this effort, the myocardium in these patients continued to rely on fatty substrates for oxidative metabolism (that is, no change in

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respiratory quotient) even though this fuel is a more costly means of producing adenosine triphosphate in terms of oxygen currency (3.93 liters oxygen/mol vs. 3.72 liters oxygen/mol for carbohydrates [14]). Even during maximal pacing, patients with syndrome X were extracting the same total amount of carbohydrate equivalents as the control subjects and, unlike control subjects, were storing rather than oxidizing this load (Fig. 3). Conversely, patients with syndrome X showed a greater uptake ($p < 0.05$) of free fatty acids than the control subjects and oxidized more lipid fuel (Fig. 4).

Mechanism of metabolic changes. The mechanism of these differential metabolic changes can be interpreted with reference to the schemes shown in Figures 5 and 6. Under normal conditions in the fasting state, the heart takes up glucose, lactate, pyruvate, ketone bodies, free fatty acids and glycerol from the circulation (Fig. 5) but uses mostly fatty substrates (both circulating free fatty acids and endogenous triglycerides) for oxidative production of energy, as indicated by a respiratory quotient of ~0.75. Although maximal pacing effort draws from carbohydrate (circulating glucose and tissue glycogen) to meet the increased energy demand, the recovery phase promptly restores a positive net balance between uptake and oxidation of carbohydrates. In syndrome X, an increased flux of lipid substrates into the Krebs cycle throughout pacing and recovery is associated with essentially unchanging rates of carbohydrate uptake and oxidation and a reversed pattern of pyruvate and alanine exchange. Increased fat oxidation generates signals (increased citrate, acetyl-coenzyme A/coenzyme A ratio, adenosine triphosphate) that inhibit two rate-limiting nonequilibrium reactions in glucose metabolism—the phosphofructokinase and the pyruvate dehydrogenase step (Fig. 6). Under these circumstances, both glycolysis and pyruvate oxidation are restrained; in fact, a tight block of pyruvate entry into the Krebs cycle results in intracellular pyruvate build-up. However, because fewer reducing equivalents are generated through anaerobic glycolysis and oxygen supply keeps pace with mitochondrial oxidation of reducing equivalents, the excess pyruvate is not converted into lactate, as classically would be the case for cellular hypoxia (19). In addition, glutamate transamination with pyruvate to produce alanine is apparently inhibited, resulting in alanine net uptake rather than release. The net uptake of a reduced substrate such as beta-hydroxybutyrate, which undergoes mitochondrial oxidation and can inhibit pyruvate dehydrogenase, is unaltered. One predicted consequence of this metabolic mode is that glucose-6-phosphate will accumulate, thereby driving glycogen synthesis.

The changes observed in patients with syndrome X are really opposite to those seen in myocardial ischemia. In the latter case, deficient oxygen supply impairs free fatty acid oxidation, depresses phosphofructokinase and pyruvate dehydrogenase and accelerates glycolysis and glycogen breakdown; the intracellular acidosis favors conversion of pyruvate into lactate and alanine, thereby promoting the loss of

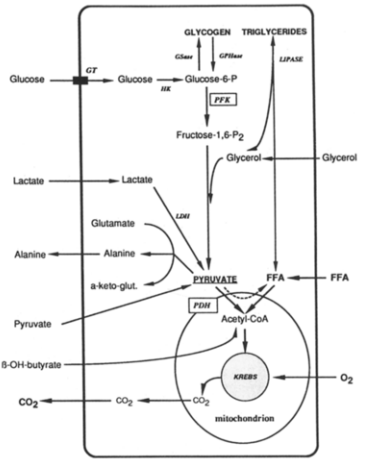

Figure 5. Normal myocardial metabolism. Under normal circumstances, glucose (whose intracellular transfer is effected by a specific transporter [GT]), lactate, pyruvate, free fatty acids (FFA), glycerol, beta-hydroxybutyrate (β-OH-butyrate) and oxygen (O_2) are taken up by cardiac muscle and alanine and carbon dioxide (CO_2) are released. Both pyruvate and free fatty acids feed the intramitochondrial acetyl-coenzyme A (CoA) pool; lipolysis and reesterification of intracellular free fatty acids may occur simultaneously and pyruvate itself may feed de novo lipid synthesis (represented as a **broken arrow** in the scheme). Key enzymes controlling intracellular fluxes of substrate interconversion and degradation are hexokinase (HK) for glucose phosphorylation, glycogen synthase (GSase) and phosphorylase (GPHase) for glycogen turnover, phosphofructokinase (PFK) for glycolytic flux, pyruvate dehydrogenase (PDH) for pyruvate oxidation and lactic dehydrogenase (LDH) for lactate-pyruvate interconversion. a-keto-glut. = alpha-ketoglutarate; P = phosphate.

unoxidized equivalents. Thus, it is difficult to fit the present information to a concept of early or minor ischemia as the basis for the metabolic changes in patients with syndrome X, particularly because these metabolic changes were already present during control conditions (when the patients were symptom free, there were no ECG changes and coronary flow was comparable with that measured in normal subjects). It would be of interest to monitor myocardial metabolism in patients with syndrome X at even higher pacing rates or after the administration of a different stressor. The occurrence of chest pain obviously limits the possibility of obtaining this kind of information.

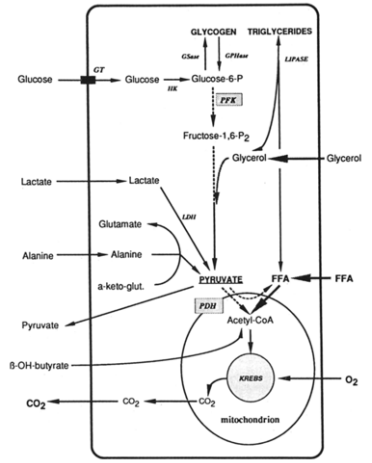

Figure 6. Myocardial metabolism in syndrome X. Excessive oxidation of lipid substrates (whether circulating or endogenous) competes with pyruvate oxidation by inhibiting pyruvate dehydrogenase (PDH) and slows down glycolysis by inhibiting phosphofructokinase (PFK). The relative excess of unused pyruvate is not massively converted into lactate or alanine because there is no acidosis (sufficient oxygen supply); rather, it is lost from the cell as such. Abbreviations as in Figure 5.

Possible Explanations and Comparison With Previous Reports

ECG changes. The ischemic ECG changes and the reduced coronary flow increment observed during pacing remain to be explained. The ECG signal is generated by electrochemical gradients established by ion fluxes across the cell membrane. The maintenance of these fluxes depends on the energy status of the cell, which in turn is determined by myocardial metabolism. For example, a typical and impressive example of how metabolic alterations influence the ECG signal can be observed after the intracoronary administration of atractyloside in the dog. This glycoside, which inhibits adenine nucleotide translocase, induces ST segment elevation indistinguishable from that observed after coronary artery ligation while simultaneously producing a significant increase in coronary flow (20).

Criteria for patient enrollment. The criteria used to enroll patients in our study were quite strict and different from those used by other investigators. This difference might explain, at least in part, some disagreement with previous reports (1,2,15). In one of the largest published series (2), 32% of patients had arterial hypertension, >3% were diabetic, 6% had mitral valve prolapse and <15% had a positive exercise stress test.

Thermodilution method to measure myocardial perfusion. A word of caution must be expressed regarding the technique used to measure myocardial perfusion in this study. We are aware of the intrinsic limitations of the thermodilution method (21). To minimize some sources of error, only great cardiac vein flow was computed because it is known that, during pacing, coronary sinus flow is affected by right atrial reflux (22). Furthermore, because syndrome X, unlike atheromatous coronary artery disease, does not seem to be a regional disturbance (as evidenced by the preserved regional and global left ventricular function during pacing), many of the limitations that apply to this technique are not relevant.

Role of patient gender. To see whether gender (12 women in the syndrome X group and 4 women and 6 men in the control group) could account for some of the metabolic differences between the two groups, we compared the baseline metabolic data from the 6 male control subjects with those from the 4 control women. Although the small size of our study group limits the inferences that can be made, no statistically significant differences were found between men and women in the control group. For example, pyruvate extraction in the control group was 44 ± 7% in control men versus 32 ± 4% in women ($p = 0.24$), whereas it was 16 ± 8% in women in the syndrome X group; alanine extraction in the control group was −3 ± 2% in control men versus −4 ± 1% in women ($p = 0.78$), whereas it was 3 ± 2% in women in the syndrome X group.

Role of blood pressure. Finally, the higher blood pressure levels measured in patients with syndrome X at the time of the invasive study (all patients were normotensive as judged from blood pressure values obtained repeatedly during 1 week of hospitalization) are probably the expression of the greater sensitivity of these patients to psychologically stressful stimuli. This is in agreement with the elevated neuroticism scores recently reported in such patients (23).

Conclusions. Patients with angiographically normal coronary arteries and exercise-induced angina and ST depression (generally labeled as having syndrome X) show a nonischemic pattern of myocardial substrate uptake and utilization both at rest and in response to pacing stress compatible with stress-induced acceleration of oxidative fat utilization. Although our results do not explain the occurrence of chest pain and ST segment depression in these patients, they cast additional light on the pathophysiology of this condition.

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